

The Tail Rank Test

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1 Introduction

OOMPA is a suite of object-oriented tools for processing and analyzing large biological data sets, such as those arising from mRNA expression microarrays or mass spectrometry proteomics.

This vignette documents the tail rank test, which provides an alternative method for discovering potential biomarkers in large data sets. The idea is that one starts with a target specificity for a gene as a univariate biomarker, and uses the “normal” or “baseline” samples to estimate a threshold that yields that specificity. Then, for each gene, one counts the number of “cancer” or “experimental” samples that exceed the gene-specific threshold. Significance is determined based on control of the family-wise error rate (FWER).

2 Getting Started

As usual, we start by loading the library.

```
> library(TailRank)
```

The *TailRank* package comes with some sample data that we can use to illustrate the methods. The sample data consists of a subset containing 2000

genes from a prostate cancer study on glass arrays reported by Lapointe and colleagues [1]. The next set of commands loads the data.

```
> data(expression.data)
> data(gene.info)
> data(clinical.info)
> dim(clinical.info)
```

```
[1] 112 6
```

There are 112 samples in the study. The `Subgroups` column of the `clinical.info` data frame refers to the subgroups discovered in the original publication by clustering based on the gene expression data. The `ChipType` column identifies the two different generations of glass arrays that were combined in the study. The `Status` column classifies the samples as normal prostate (N), primary prostate tumor (T), or lymph node metastasis (L). Since there is a natural order to this status in terms of the severity of the disease, we are going to make certain that it is used:

```
> clinical.info$Status <- ordered(clinical.info$Status, levels = c("N",
+ "T", "L"))
> summary(clinical.info)
```

Arrays	Reference	Sample	Status	Subgroups	ChipType
p16090 : 1	CRG1 : 1	PL114 : 1	N:41	I :11	new:86
p16093 : 1	CRG10 : 1	PL115 : 1	T:62	II :39	old:26
p16095 : 1	CRG100 : 1	PL116 : 1	L: 9	III:19	
p16097 : 1	CRG101 : 1	PL118.3: 1		N :41	
p16098 : 1	CRG102 : 1	PL122 : 1		0 : 2	
p16101 : 1	CRG103 : 1	PL129 : 1			
(Other):106	(Other):106	(Other):106			

3 Performing the Tail Rank Test

The main function in the package is the `TailRankTest`. We start by invoking this function with the default values of the arguments. The summary includes details on the parameters that were used, along with the fact that 49 of the 2000 genes were more highly expressed in non-normal samples than would be expected by chance, based on a 5% FWER.

```
> trt <- TailRankTest(expression.data, clinical.info$Status)
> summary(trt)
```

```
A tail-rank test object in the up direction.
The test was performed using the bb model.
Specificity: 0.95 computed with tolerance 0.5
Significance cutoff: 24 based on a family-wise error rate less than 0.05
There are 49 tail-rank statistics that exceed the cutoff
```

In the next example, we increase both the target specificity (from the default of 95% to a desired value of 99%) and the desired confidence limits (to 99% from the default of 95%). With this more stringent criteria, only 25 of the genes remain significant.

```
> trt2 <- TailRankTest(expression.data, clinical.info$Status, specificity = 0.99,
+   confidence = 0.99)
> summary(trt2)
```

```
A tail-rank test object in the up direction.
The test was performed using the bb model.
Specificity: 0.99 computed with tolerance 0.5
Significance cutoff: 19 based on a family-wise error rate less than 0.01
There are 25 tail-rank statistics that exceed the cutoff
```

3.1 Which genes are significant?

After performing an analysis that identifies a gene list like this, it is, of course, natural to want to know which genes were selected. The `as.logical` method converts the results of the tail rank test into a logical vector that selects these significant genes. Using this method, we can verify that the 25 genes selected by the more stringent criteria are a subset of the 49 genes selected using the weaker criteria.

```
> sel <- as.logical(trt)
> sel2 <- as.logical(trt2)
> sum(sel2 & sel)
```

```
[1] 25
```

Since this vector serves as index into the `gene.info` database, we can figure out which genes were actually selected.

```
> gene.info[sel2, 3:6]
```

	Clone.ID	Gene.Symbol	Cluster.ID	Accession
X2180	IMAGE:506669	LOC170394	Hs.157728	AA708916
X23774	IMAGE:244350		Hs.484965	N54811
X5918	IMAGE:26883			
X11386	IMAGE:302331	MYL4	Hs.356717	AI668645
X27346	IMAGE:376764	UTRN	Hs.250607	AA046146
X26538	IMAGE:364934	DAPK1	Hs.244318	AA024655
X17798	IMAGE:838829	PLU-1	Hs.143323	AA464869
X7405	IMAGE:814528	TP53INP1	Hs.75497	AA459364
X27228	IMAGE:47475	CYFIP2	Hs.211201	H12043
X40508	IMAGE:811582		Hs.459841	AA454597
X12648	IMAGE:809421	PCBD	Hs.3192	AA442959
X17040	IMAGE:258175		Hs.23754	N30900

X12642	IMAGE:788667	FAPP2	Hs.233495	AA449847
X39564	IMAGE:306806	FLJ31434	Hs.7988	N91900
X38876	IMAGE:609155	LRRN1	Hs.512663	AA176867
X181	IMAGE:854696	SIAHBP1	Hs.74562	AA630094
X32626	IMAGE:263846	PPP2R1B	Hs.431156	H99771
X13168	IMAGE:129865	STK6	Hs.250822	R11407
X31785	IMAGE:259374	MCCC2	Hs.167531	N31952
X13736	IMAGE:2012757	D2S448	Hs.118893	AI356709
X31836	IMAGE:141815	JAG1	Hs.409202	R70684
X33578	IMAGE:288663	GJB1	Hs.333303	N62394
X10735	IMAGE:882459	PPIC	Hs.110364	AA676404
X5726	IMAGE:447569	RNPC2	Hs.282901	AA702428
X12019	IMAGE:126415		Hs.133130	R06581

4 Power Computations

The power depends on the number of genes (G), the number of healthy samples (N_1), the number of cancer samples (N_2), the target specificity (ψ), the confidence ($\text{conf} = 1 - \text{FWER}$), and the sensitivity that you want to be able to detect (ϕ). Here is an example using the sizes from the prostate cancer data set, showing that we have more than 70% power to detect a marker with 40% sensitivity.

```
> tailRankPower(2000, N1 = 41, N2 = 71, psi = 0.95, phi = 0.4,
+   conf = 0.95)
```

```
[1] 0.7135006
```

The next example shows that the power decreases to 43% when using the same number of samples with a whole genome array containing 40000 gene probes. (This was the size of the full study from which these 2000 genes were randomly selected.)

```
> tailRankPower(40000, N1 = 41, N2 = 71, psi = 0.95, phi = 0.4,
+   conf = 0.95)
```

```
[1] 0.4271892
```

We can determine the power for a variety of cancer sample sizes, keeping everything else the same

```
> tailRankPower(40000, N1 = 41, N2 = seq(40, 100, by = 10), psi = 0.95,
+   phi = 0.4, conf = 0.95)
```

```
[1] 0.2063922 0.3067931 0.3920020 0.4033145 0.4648195 0.4673351 0.5137604
```

More generally, we can create power tables using the `biomarkerPowerTable` function. Individual tables have rows labeled by the number of “cancer” samples and columns labeled by the desired sensitivity; the entries in the table show the power to detect that level of sensitivity when using that many samples.

```
> biomarkerPowerTable(G = c(10000, 20000, 40000), N1 = 41, N2 = seq(40,  
+   100, by = 10), psi = 0.95, conf = 0.95, phi = seq(0.3, 0.5,  
+   by = 0.05))
```

```
[[1]]  
An object of class "BMPT"  
Slot "G":  
[1] 10000  
  
Slot "psi":  
[1] 0.95  
  
Slot "conf":  
[1] 0.95  
  
Slot "power":  
      30      35      40      45      50  
40 0.09033665 0.1991811 0.3571932 0.5409076 0.7144119  
50 0.12613959 0.2663173 0.4525563 0.6462431 0.8062082  
60 0.12068814 0.2640932 0.4577585 0.6584144 0.8203311  
70 0.14804875 0.3129456 0.5212980 0.7202351 0.8659786  
80 0.17247308 0.3543683 0.5716972 0.7654303 0.8962882  
90 0.19413312 0.3895314 0.6121234 0.7992573 0.9171966  
100 0.21332331 0.4195350 0.6449771 0.8251594 0.9321230
```

```
[[2]]  
An object of class "BMPT"  
Slot "G":  
[1] 20000  
  
Slot "psi":  
[1] 0.95  
  
Slot "conf":  
[1] 0.95  
  
Slot "power":  
      30      35      40      45      50  
40 0.05886264 0.1420590 0.2765896 0.4504793 0.6328099  
50 0.09058714 0.2069445 0.3772638 0.5720731 0.7487870
```

```
60 0.12068814 0.2640932 0.4577585 0.6584144 0.8203311
70 0.11639120 0.2621789 0.4617095 0.6678071 0.8309751
80 0.14046885 0.3057095 0.5182606 0.7220098 0.8698565
90 0.16239855 0.3434290 0.5642925 0.7629450 0.8967688
100 0.15428558 0.3344203 0.5581562 0.7609404 0.8972354
```

```
[[3]]
An object of class "BMPT"
Slot "G":
[1] 40000
```

```
Slot "psi":
[1] 0.95
```

```
Slot "conf":
[1] 0.95
```

```
Slot "power":
          30          35          40          45          50
40 0.03682533 0.09740169 0.2063922 0.3628918 0.5449930
50 0.06324274 0.15651685 0.3067931 0.4956936 0.6837994
60 0.09038819 0.21232817 0.3920020 0.5948291 0.7729542
70 0.09001682 0.21627298 0.4033145 0.6121954 0.7908250
80 0.11292231 0.26053337 0.4648195 0.6752875 0.8392830
90 0.11006564 0.25911220 0.4673351 0.6813917 0.8459462
100 0.12947138 0.29490766 0.5137604 0.7248561 0.8757409
```

5 References

[1] Lapointe J et al. (2004) Gene expression profiling identifies clinically relevant subtypes of prostate cancer. *Proc Natl Acad Sci U S A*, 101, 811–816.